REMARKS

Claims 15 and claims 17-32 and new claims 33-35 are pending.

The amendments and new claims are supported in the specification as follows: Claim 1: (p.33, line 1; p.37, line 2); Claim 33:(p.33, line 1); Claim 34: (p.33, line 2) and Claim 35: (p.30, line 2).

Applicants acknowledge the election of claims without traverse.

Claim rejections under 35 USC § 103

Claims 15, 17-20, 22, 24, 26, 28 and 30-32 are rejected under U.S.C. 103(a) as being unpatentable over Kimura *et al. (Chem. Pharm. Bull.* (2001); 49(10): 1321-1325) in view of Postma *et al.* (Am J Respir Crit Care Med. (1998); 158(5 Pt 3): S187-92).

The applicants respectfully disagree with the rejection.

Disclosure of Kimura & Postma

The Office Action specifically cites the second sentence in the first paragraph on page 1321 of Kimura where the reference mentions that TA-270 (compound No. 551) inhibits the immediate- and late-airway responses, pulmonary inflammatory cell accumulation, and airway hypersensitiveness (hereinafter, "hypersensitiveness" is considered to be a synonymous term for "hyper-responsiveness" recited in the present specification and Declaration"). The context refers to the first sentence in the same paragraph. This means that, Kimura discloses that compound No. 551 is effective as an anti-allergic compound whose pharmacological mechanism is apparently based on inhibitory effects on immediate-and late-airway responses, pulmonary inflammatory cell accumulation, and airway hypersensitiveness resulting from an antigen-antibody reaction

(so-called allergic reaction). The disclosure of the sentence is a citation from Aoki *et al.* *(European Journal of Pharmacology* 409 (2000): 325-330).

More specifically, Aoki *et al.* disclose that compound No. 551 significantly inhibits an increase of eosinophils among inflammatory cells and that the compound improves antigen-induced airway hypersensitiveness on a guinea pig asthma model where an antigen-antibody reaction is induced (See Table 1 and lines 1-4 of page 328). Additionally, Aoki *et al.* describes the tendency to inhibit the infiltration of total cells, macrophages and neutrophils although the tendency is quite moderate as shown in Table 1 on page 328.

In this point, Postma *et al.* disclose that "[e]osinophils have been reported to be present in chronic bronchitis, in particular during exacerbations of the disease" (see lines 3-5 of the right column of page S189). However, the reference also discloses that "[i]t has been suggested that, in contrast to asthma, the tissue eosinophils found in COPD do not degranulate and are not associated with an increased expression of interleukin (IL)-5" (see lines 5-8 in the same column).

Since the types or mode of inflammatory cells present between asthma (allergic reaction) and COPD vary, in fact, whether compound No. 551 of the claimed invention exhibits therapeutic effects in treating COPD, or how much therapeutic effects of compound No. 551 can achieve in treating COPD (i.e. therapeutic effects presented in Declaration, as described below) would be at least unexpected by those skilled in the art at the time of the invention. Nevertheless, it was asserted in the rejection that the disclosure of Kimura *et al.* (Aoki *et al.)* motivates those skilled in the art to use compound No. 551 for treating COPD in view of Postma.

However, as discussed below, the therapeutic effects of the compounds of the claimed invention are not based on the inhibitory effects of the compound on the increase of inflammatory cells, as disclosed by Kimura *et al.* or Aoki *et al.*

Difference in pharmacology between asthma and COPD

Although COPD and asthma have common symptoms such as air-way inflammation, and air flow limitation, they have different mechanisms that exhibit the symptoms. Asthma, classified as an allergic disease, exhibits airway inflammation and airway hypersensitiveness due to endogenous allergic inflammation where endogenously-produced antibodies react with a specific antigen. On the other hand, it is known that 90% or higher of episodes of COPD has been caused from smoking. Specifically, airway inflammation and airway hypersensitiveness are caused directly by exogenous toxic substances contained in, for example, cigarette smoke in COPD. In addition, the pathogenesis of asthma has been clarified in large part. Therefore, many drugs for treating asthma have been developed. However, the pathogenesis of COPD has not been sufficiently elucidated. Accordingly, commercially-available drugs for COPD are limited. In this point, it is more difficult for those skilled in the art to develop a drug for treating COPD, compared to a drug for treating asthma.

As a candidate for such a toxic substance, peroxynitrite ($ONOO^-$) has been reported (see Am J Respir Crit Care Med Vol. 162. pp 701-706, 2000). In COPD patients, deterioration in respiratory function has 'relevance to the amount of nitrotyrosine (NT), namely a biomarker of peroxynitirite in the airway tracts. However, it is known that such a relevance cannot be observed in asthma patients. Therefore, in Examples of the present specification, compounds of the claimed invention were

evaluated on an airway hypersensitiveness model of a guinea pig where peroxynitrite was exposed to the airway tracts to induce such airway impairment.

In order to clarify a difference between drug effects on an asthma model using antigen stimulation and on a COPD model using an exogenous toxic substance, the Applicants evaluated a commercially-available asthma drug "Pranlukasut", which improved accumulation of inflammatory cells in the airway tract and airway hypersensitiveness in an asthma guinea pig model (Eur. J. Phairmacol. 409), on the peroxynitirite-exposed model. The results are presented as Experiment 1 in the attached Declaration.

As shown in FIG. 1 on page 1 of the Declaration, Pranlukast did not exhibit therapeutic effects on airway hypersensitiveness in the COPD animal model while the drug exhibited significant therapeutic effects on airway hypersensitiveness in the asthma model.

Thus, even if a compound can improve accumulation of inflammatory cells in airway tracts and airway hypersensitiveness in the asthma model using antigen stimulation, it would be unobvious to those skilled in the art whether such a compound exhibits therapeutic effects in treating COPD due to the direct exogenous stimulation. Meanwhile, compound 551 showed unexpected and remarkable improvement effects on the peroxynitirite-exposed model that can not been improved by Pranlukast.

Unexpected therapeutic effects of compound No. 551 on COPD

Nevertheless, the rejection asserted that the inhibitory effect on inflammatory cells disclosed by Aoki *et al.* (cited by Kimura *et al.)* motivates those skilled in the art to use

compound No. 551 for treating COPD in view of Postma. The Applicants disagree and to rebut the conclusion, the Applicants conducted an experiment to demonstrate unexpected therapeutic effects of compounds of the present invention. This is presented as Experiment 2 in the attached Declaration.

As described above, 90% or higher of episodes of COPD are caused from smoking, and it is well known that the symptoms thereof are further aggravated by infection in the upper airway tract. Based on the fact, the Applicants formulated a pulmonary emphysema model (i.e. COPD model) of a guinea pig whose airway tracts were exposed to a cigarette smoke solution and lipo-polysaccharide (LPS) that was an inflammatory substance derived from bacteria day by day. In this model, vacuolation was observed in alveoli of the lung, and it was confirmed that the airway resistance and residual volume were increased (see FIG. 2 in Declaration). Accordingly, it was evident that pulmonary emphysema was induced in this model.

The Applicants evaluated therapeutic effects of compound No. 551 and Theophyline (a commercially-available drug used for treating asthma and COPD) on the above-described emphysema model. With regard to airway resistance that corresponds to FEV1 in clinical evaluation, both compound No. 551 and theophyline exhibited the same level of the improving effects. However, with regard to the increase in the residual volume that is characterized in COPD, the commercial drug "theophyline" did not exhibit improving effects while compound No. 551 exhibits significant therapeutic effects in this pulmonary emphysema model.

Thus, the Applicants demonstrated the remarkable therapeutic effects of compound No. 551 on the increase of the residual volume that cannot be expected on the above-mentioned asthma model, and the therapeutic effects of the claimed invention are remarkable over commercial drugs such as theophyline.

In order to confirm whether the above-described therapeutic effects of compound No. 551 on the pulmonary emphysema model are based on its inhibitory effects on the increase in inflammatory cells, the Applicants further conducted Experiment 3 described in the attached Declaration.

Immediately after pulmonary function was evaluated on the pulmonary emphysema model, the number of each inflammatory cell was counted by the method described in the Declaration. As shown in FIG. 4, the number of eosinophils was not influenced by administering compound No. 551. The other inflammatory cells were also not affected by the administration thereof although they had a tendency of the suppression. That is, the data at least suggest that the therapeutic effects of compound No. 551 are not based on the inhibitory effects on the increase of inflammatory cells in COPD.

Since Aoki *et al.* (cited by Kimura *et al.)* disclose that compound No. 551 significantly inhibits the increase of eosinophils on the antigen-induced asthma model, and discuss that eosinophils has been suggested as playing an important role in airway hyper responsiveness. Based on the disclosures of the cited references and the empirical data of the Experiments in the Declaration, the therapeutic effects of the compounds of the present invention would indeed be **unexpected** by those skilled in the art at the time of the invention.

Contribution of the present invention to the prior arts

"CHEST 1999; 115: 68-74" describes that a residual volume is a parameter specific to COPD other than asthma (see line 11 on page 71). "CHEST 1999; 115: 160-165" further reports that a single administration of theophyline cannot exhibit therapeutic effects on the increase in the residual volume in COPD patients, as also demonstrated in Experiment 2 of

Declaration. In general, β_2 agonists, anticholinergics, and theophyline are used mainly for treating COPD, and β_2 agonists and anticholinergics are a type of inhalant. This is because such drugs will exhibit strong side effects if the drugs are administered systemically by way of oral administration or the like, and local administration is appropriate for such drugs. In this point, there is a disadvantage in which it is difficult to administer such inhalants compared to oral medications. On the other hand, in fact, theophyline is a type of oral medication for treating COPD. However, as demonstrated above, the drug cannot achieve therapeutic effects on the increase of the residual volume. Additionally, steroid drugs may be combined during exacerbations of the disease, and the drugs are also a type of inhalant to prevent the side effects.

Concerning the above-described current COPD therapy, the compounds of the claimed invention can be prepared as an oral medication that can be easily administered to COPD patients, and have remarkable therapeutic effects that improve the increase in the residual volume characterized in COPD.

Thus, the COPD therapy using the compounds of the present invention can solve the difficulties in treating COPD, and will bring about significant contributions to current medical care in treating COPD.

Additionally, Claim 1 is not limited to oral administration excluding inhalation (i.e. Claim 33) because the claimed compounds are still effective as an inhalant, and the effectiveness is unexpected over the prior arts, as discussed above. Furthermore, the way of administration can include the other types of administration described on page 33. This is because the effects of the present invention can be reasonably expected, for example, in intravenous administration, subcutaneous administration or the like other than oral administration in view of Examples and Experiments in Declaration, and choice of the type of administration would be a matter of a physician's diagnosis.

It is respectfully requested that the rejection be reconsidered and withdrawn in light of the above explanation and attached empirical evidence.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

By _____
James E. Armstrong, IV
Registration No.: 42,266
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(202) 478-7375
Attorneys/Agents For Applicant

Attachment: Declaration Pursuant to 37 C.F.R. 1.132